Acyclovir

Brand Name: Zovirax

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Drug Description

Acyclovir is a synthetic purine nucleoside analogue antiviral agent derived from guanine. [1]

HIV/AIDS-Related Uses

Oral acyclovir is approved by the FDA for the treatment of initial and frequently recurrent episodes of herpes simplex and genital herpes (HSV-1 and HSV-2) infection in immunocompromised patients. Parenteral acyclovir is approved for the treatment of initial or recurrent HSV infections and herpes zoster infections (shingles) caused by varicella-zoster virus (VZV) in immunocompromised patients. Off-label uses of both oral and parenteral acyclovir include use in the prophylaxis of HSV and herpes zoster infections and treatment for herpes zoster opthalmicus.[2] Topical acyclovir is approved for treatment of initial episodes of genital herpes and HSV infections in immunocompromised patients; however, systemic acyclovir is more effective and may be preferred.[3]

Non-HIV/AIDS-Related Uses

Oral acyclovir is approved for treatment of initial or frequently recurrent genital herpes infection and herpes zoster infections (shingles) and adult varicella infections (chickenpox) caused by VZV. It is not recommended for use in the treatment of uncomplicated chickenpox in healthy children. Parenteral acyclovir is approved for severe initial episodes of genital herpes infection, neonatal HSV infections, and herpes simplex encephalitis in immunocompetent patients.[4]

Pharmacology

Acyclovir inhibits HSV and VZV both in vitro and vivo by interfering with DNA synthesis and inhibiting viral replication. Acyclovir is converted to acyclovir triphosphate by cellular kinases and is highly specific for thymidine kinase (TK) encoded by HSV and VZV. The activated phosphorylated form of acyclovir stops replication of herpes viral DNA by competitive inhibition of viral DNA polymerase, incorporation and termination of viral DNA chain and inactivation of the viral DNA polymerase.[5] [6]

Acyclovir's absorption from the gastrointestinal (GI) tract is variable and incomplete; it is estimated that 10%-30% of an oral dose of the drug is absorbed. Some data suggest that GI absorption of acyclovir may be saturable; in healthy adults, the extent of absorption decreased with increasing dose. Food does not appear to affect acyclovir's absorption. Peak plasma concentration of acyclovir usually occurs within 1.7 hours after oral administration and after the end of infusion with intravenous (IV) administration.[7] [8]

Acyclovir is widely distributed into body tissues and fluids, including the brain, kidney, saliva, lung, liver, muscle, spleen, uterus, vaginal mucosa and secretions, cerebrospinal fluid (CSF), herpetic vesicular fluid, and semen. The apparent volume of distribution of acyclovir is reported to be 32.4 to 61.8 L/1.73 m2 in adults. Following IV infusion, acyclovir generally diffuses well into CSF; in patients with uninflamed meninges, CSF concentrations of acyclovir are reported to be approximately 50% of concurrent serum acyclovir concentrations.[9]

Acyclovir is in FDA Pregnancy Category B. There are no adequate and well-controlled studies of acyclovir in pregnant women. When administered to mice, rabbits, and rats during organogenesis, acyclovir was not teratogenic. Acyclovir did not impair fertility or reproduction in mice or in rats, though at higher doses implantation efficacy decreased in rats and rabbits. Acyclovir crosses the placenta. Limited data indicate that the drug is distributed into milk, generally in concentrations greater than concurrent maternal plasma concentrations, possibly via an active transport mechanism. As a result, acyclovir should be administered to nursing mothers with caution and only when indicated.[10]

In vitro, acyclovir is approximately 9% to 33% bound to plasma proteins at drug concentrations of 0.41 to 52 mcg/ml. In adults with normal renal function, the half-life of oral acyclovir averages 2.5 to 3.3 hours and the half-life of parenteral acyclovir

Acyclovir

Pharmacology (cont.)

averages 2.5 hours. Acyclovir is excreted principally in urine via glomerular filtration and tubular secretion; most of a single IV dose of the drug is excreted in urine as unchanged drug within 24 hours of administration. Limited data suggest that peritoneal dialysis and blood exchange transfusions do not appreciably remove the drug. Hemodialysis reduces plasma concentrations of acyclovir by about 60%. Doses and frequency of administration of the drug should be modified according to creatinine clearance and age.[11] [12]

Resistance to acyclovir can result from qualitative and quantitative changes in viral TK and/or DNA polymerase. Clinical isolates of HSV and VZV with reduced susceptibility to acyclovir have been recovered from immunocompromised patients, especially those with advanced HIV infection. Most acyclovir-resistant mutants are TK-deficient; these TK-negative mutants may cause severe disease in infants and immunocompromised adults. The possibility of viral resistance to acyclovir should only be considered in patients who show poor clinical response during therapy.[13]

Adverse Events/Toxicity

Adverse reactions generally have been minimal following oral or IV administration of acyclovir. However, potentially serious reactions (e.g., renal failure, thrombotic thrombocytopenic purpura) can occur and may be fatal.[14] The most frequent adverse effects observed with use of acyclovir are phlebitis (inflammation at the injection site with parenteral acyclovir), acute renal failure, encephalopathy, hematologic abnormalities, thrombocytopenia or thrombocytosis, hematuria, and urticaria.[15]

During clinical trials, the most frequent adverse events reported were nausea, vomiting, diarrhea, headache, and malaise.[16]

Drug and Food Interactions

Dosage adjustment is recommended when administering acyclovir to patients with renal impairment or to patients receiving potentially nephrotoxic agents; acyclovir may increase the risk of renal dysfunction and/or the risk of reversible central nervous system symptoms such as those that have been reported in patients treated with IV acyclovir.[17]

Amphotericin B has been shown to strengthen the antiviral effect of acyclovir against pseudorabies virus in vitro. Interferon has also shown additive or synergistic antiviral effect with acyclovir in vitro against HSV-1 cultures. The clinical importance of these interactions are not known. Drugs with the potential for clinically significant interaction with acyclovir include antifungal agents, probenecid, interferon, methotrexate, and zidovudine.[18]

Food does not appear to affect acyclovir's absorption.[19]

Contraindications

Acyclovir is contraindicated in patients with hypersensitivity to acyclovir or valacyclovir.[20]

Clinical Trials

For information on clinical trials that involve Acyclovir, visit the ClinicalTrials.gov web site at http://www.clinicaltrials.gov. In the Search box, enter: Acyclovir AND HIV Infections.

Dosing Information

Mode of Delivery: Oral (tablet, capsule, or suspension), intravenous, or topical.[21]

Dosage Form: Acyclovir capsules containing 200 mg; acyclovir tablets containing 400 mg and 800 mg; acyclovir oral suspension, banana-flavored, containing 200 mg acyclovir per teaspoonful (5 ml).[22]

Acyclovir sodium for injection in 10-ml sterile vials, each containing the equivalent of 500 mg acyclovir and in 20-ml sterile vials, each containing the equivalent of 1000 mg acyclovir.[23]

Acyclovir 5% topical ointment contains 50 mg acyclovir in a polyethylene glycol base; available in 3 g and 15 g tubes.[24]

Storage: Acyclovir capsules, tablets, and

Acyclovir

Dosing Information (cont.)

suspension should be stored at temperatures between 15 C to 25 C (59 F to 77 F) and protected from moisture.[25]

Acyclovir sodium for injection should be stored at temperatures between 15 C to 25 C (59 F to 77 F).[26]

Acyclovir 5% topical ointment should be stored at temperatures between 15 C to 25 C (59 F to 77 F) in a dry place.[27]

Chemistry

CAS Name: 6H-Purin-6-one,2-amino-1,9-dihydro-9-((2-hydroxyethoxy)methyl)-[28]

CAS Number: 59277-89-3 (Acyclovir)[29]

69657-51-8 (Acyclovir sodium)[30]

Molecular formula: C8-H11-N5-O3 (Acyclovir) / 247.19 (Acyclovir sodium)[31]

C42.67%, H4.92%, N31.10%, O21.31% (Acyclovir) / C38.87%, H4.08%, N28.33%, O19.41%, Na9.30% (Acyclovir sodium)[32]

Molecular weight: 225.20 (Acyclovir) / 247.19 (Acyclovir sodium)[33]

Melting point: 256.5 to 257 C (Acyclovir)[34]

Physical Description: White crystalline powder (Acyclovir).[35]

White crystalline lyophilized powder (Acyclovir sodium).[36]

Stability: Once diluted for administration, each dose of acyclovir sodium for injection should be used within 24 hours.[37]

Solubility: Acyclovir has a maximum solubility of 2.5 mg/ml in water at 25 C at neutral pH.[38]

Acyclovir sodium has a maximum solubility of greater than 100 mg/ml in water at 25 C at neutral pH, but at physiologic pH and 37 C, the drug is almost completely un-ionized and has a maximum solubility of 2.5 mg/ml.[39]

Other Names

Aciclovir[40]

Acycloguanosine[41]

BW-248U[42]

ACV[43]

Wellcome-248U[44]

Acyclovir Sodium[45]

Genvir[46]

Virolex[47]

Further Reading

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For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

• Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET

• Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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